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Regression of coronary atherosclerosis: Current evidence and future perspectives

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ABSTRACT

Coronary atherosclerosis has been considered a chronic disease characterized by ongoing progression in response to systemic risk factors and local pro-atherogenic stimuli. As our understanding of the pathobiological mechanisms implicated in atherogenesis and plaque progression is evolving, effective treatment strategies have been developed that led to substantial reduction of the clinical manifestations and acute complications of coronary atherosclerotic disease. More recently, intracoronary imaging modalities have enabled detailed *in vivo* quantification and characterization of coronary atherosclerotic plaque, serial evaluation of atherosclerotic changes over time, and assessment of vascular responses to effective anti-atherosclerotic medications. The use of intracoronary imaging modalities has demonstrated that intensive lipid lowering can halt plaque progression and may even result in regression of coronary atheroma when the highest doses of the most potent statins are used. While current evidence indicates the feasibility of atheroma regression and of reversal of presumed high-risk plaque characteristics in response to intensive anti-atherosclerotic therapies, these changes of plaque size and composition are modest and their clinical implications remain largely elusive. Growing interest has focused on achieving more pronounced regression of coronary plaque using novel anti-atherosclerotic medications, and more importantly on elucidating ways toward clinical translation of favorable changes of plaque anatomy into more favorable clinical outcomes for our patients.

Key Words: Atherosclerosis, Regression, Statin, Vulnerable plaque.

Introduction

Atherosclerosis is a chronic disease that advances over time by accumulation of atheromatous plaque within the vessel wall in response to arterial injury and systemic risk factors. Advances in our understanding of the complex pathobiology of atherosclerosis have led to the development of interventions that effectively reduce the clinical manifestations of coronary atherosclerotic disease including angina or acute coronary thrombosis [1,2]. In addition to their documented efficacy for prevention of recurrent cardiac events, anti-atherosclerotic medications including lipid-lowering drugs [3–5], antihypertensive medications [6], and investigational anti-inflammatory agents [7] have shown the potential to favorably affect the development and progression of coronary plaque—i.e., the anatomical substrate of ischemic coronary events. The effect of statins, in particular, to halt the progression of coronary atherosclerosis and to induce modest disease regression when high-intensity lipid-lowering agents are administered [4,5,8] represents an important milestone in cardiovascular medicine. The process of atheroma regression is not only refined to reduction of plaque size but may also include favorable changes of plaque morphology and composition. Novel *in vivo* intracoronary imaging modalities have provided important insights into the natural history of

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coronary atherosclerosis and enabled the assessment of plaque stabilization and regression in response to potent anti-atherosclerotic medications.

Coronary imaging for *in vivo* plaque quantification and characterization

Intravascular ultrasound for quantification of coronary atheroma

Coronary angiography has been the gold standard for clinical assessment of obstructive coronary artery disease (CAD). Nonetheless, the obtained lumenography inherently ignores the atherosclerotic changes occurring within the vessel wall and does not account for the arterial wall's remodeling response to the developing plaque [9]. Intravascular ultrasound (IVUS) is based on acoustic sound wave backscattering. The amplitude of the reflected ultrasound wave is used to create the gray-scale image resulting in a axial resolution of 80–120 μm and a penetration depth of 4–8 mm. IVUS enables the acquisition of tomographic images of the entire coronary vessel wall and allows for accurate, reproducible quantification of atheroma burden *in vivo* [10]. IVUS performed serially at consecutive time points represents the gold standard for assessment of plaque progression or regression over time and thereby provides the basis for an *in vivo* evaluation of the effect of anti-atherosclerotic medications [10]. Plaque burden in a two-dimensional IVUS frame is expressed by the ratio of plaque plus media area divided by vessel area. Volumetric (three-dimensional) measures of disease burden include total atheroma volume (TAV), i.e., the sum of atheroma area measured in sequential cross-sectional frames and percent atheroma volume (PAV), i.e., the percent of the vessel volume occupied by atheroma. PAV has been the primary endpoint in the majority of serial IVUS studies [3–8,11–13].

Intracoronary imaging technologies for in vivo assessment of plaque morphology and composition

Pathological studies have identified characteristics of plaque composition that are linked to a lesion's likelihood to rupture and cause an acute coronary event [14]. A high-risk, vulnerable plaque typically refers to a lipid-rich, inflamed atheroma with a thin fibrous cap covering a large necrotic core. Imaging modalities with the ability to characterize compositional aspects of coronary atheroma *in vivo* include IVUS-virtual histology (VH), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS).

IVUS-VH uses radiofrequency signals to derive plaque components. The latter are defined as necrotic core, fibro-fatty tissue, fibrous tissue, or dense calcium; accordingly, lesions are classified as pathologic intimal thickening, fibrotic plaques, fibrocalcific plaques, thin- or thick-cap fibroatheromas [15]. Validation studies have reported good correlation against human plaque histology [16–18]. Only one experimental study in pigs disputed this correlation [19], which may relate to histological differences between porcine vs. human CAD [20], and the fact that IVUS-VH algorithms have been developed and validated on human plaques. Overall, existing evidence indicates satisfactory accuracy of IVUS-VH, but one needs to keep in mind that it likely remains an imperfect surrogate of true histology and is affected by inter-observer variability and differences in definitions [21]. The axial resolution of OCT is 10-fold higher compared with IVUS; this comes at the cost of a limited axial penetration depth (1–4 mm), which renders the assessment of plaque burden nearly impossible in the presence of a lipid-rich plaque. OCT has been validated against histology for accurate measurement of fibrous cap thickness and tissue composition, and also for detection of macrophages that appear as signal-rich bands with a sharp shadow [22,23]. NIRS shows high correlation with histopathology for lipid detection with a sensitivity and specificity of >90% [24] but has the limitation that the derived "chemogram" provides compositional and no structural information. On the other hand, unlike IVUS-VH and OCT which require image interpretation for plaque characterization, NIRS provides automated lipid-core detection, thereby theoretically facilitating its real-time use for detection of lipid-rich lesions during cardiac catheterization. Overall, these modalities each feature certain advantages and limitations (Table 1) and reveal only partial aspects of plaque morphology and composition. Combined use of intracoronary imaging tools can provide substantial incremental information for *in vivo* characterization of coronary lesions compared with the information obtained by each modality alone [25]. Fig. 1 shows a representative example of different lesion types imaged with IVUS, IVUS-VH, and OCT.

Evidence of plaque regression under high-intensity statin therapy

In the past decade, serial IVUS studies demonstrated the ability of lipid-lowering therapy to slow the progression of coronary atheroma and to achieve modest plaque regression with very high doses of potent statins that substantially reduce LDL-C levels. The REVERSAL study compared the impact of moderate lipid lowering with pravastatin 40 mg vs. intensive lipid lowering with atorvastatin 80 mg on coronary atherosclerosis in stable CAD patients. In patients treated with the highest approved dose of atorvastatin, lower LDL-C levels (79 ± 30 mg/dl) were associated with prevention of plaque progression (ΔPAV + 0.2%), whereas in pravastatin-treated patients higher on-treatment LDL-C levels (110 ± 26 mg/dl) resulted in continuous plaque progression by IVUS over a 18-month follow-up (ΔPAV + 1.6%) [3]. ASTEROID was the first large-scale serial IVUS study to document modest plaque regression in the coronary arteries. In stable CAD patients treated with the highest dose of rosuvastatin (40 mg) over 24 months, reduction of LDL-C to 61 ± 20 mg/dl and increase of HDL-C to 49 ± 13 mg/dl were associated with a median PAV reduction of −0.79% (−1.21 to −0.53, $p < 0.001$) [4]. The SATURN study subsequently compared the efficacy of rosuvastatin 40 mg vs. atorvastatin 80 mg and observed a similar magnitude of plaque regression [−1.22% (−1.19 to 0.63) vs. −0.99% (−1.52 to −0.90)] with the two high-intensity statin regimens [5]. Table 2 summarizes major serial IVUS studies reporting statin-mediated plaque regression.